REMARKS

Original claims 5, 7-10, 13-38, and 40-50 were cancelled without prejudice or disclaimer.

Pursuant to 37 C.F.R. §§ 1.121(b), the current amendments to the specification and claims are also identified in marked up versions of the same attached hereto as Exhibit A and Exhibit B, respectfully, with all changes shown by conventional marking system or instructed changes. A copy of the pending claims is attached hereto as Exhibit C.

A check for $824.00 has been submitted to cover the cost for filing this application with these amended claims. No additional fees are believed due. However, if any additional fees are necessary, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0540.

Applicants believe claims 1-4, 6, 11, 12, 39 are patentable and in condition for allowance. The claim is supported in the specification, and the original claims as filed.

Furthermore, Applicants are not aware of any prior art that has all of the elements of the claims or which in proper combination with other prior art would provide all of the elements of the claims.

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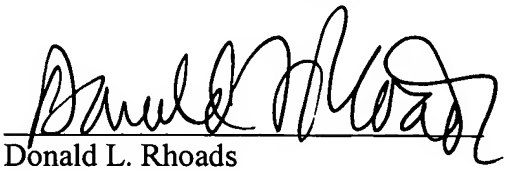
In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance and such action is earnestly solicited.

RESPECTFULLY SUBMITTED



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Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

EXHIBIT A
MARKED UP VERSION OF AMENDMENT TO THE SPECIFICATION

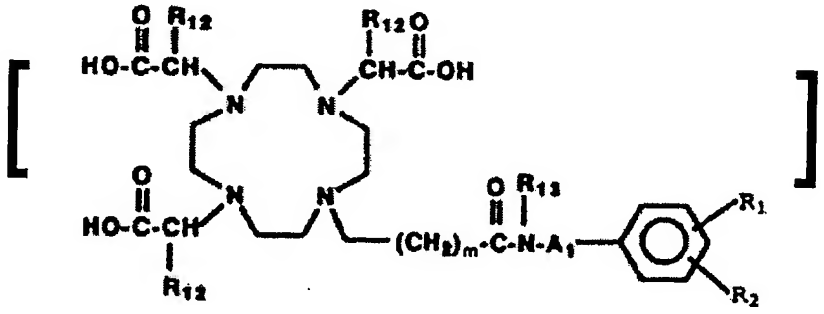
Page 1, lines 4-6:

This application is [claiming] a continuation of U.S. Application Serial No. 09/410,984, filed October 1, 1999, which is divisional of U.S. Application Serial No. 08/856,657, filed May 15, 1997, now U.S. Patent No. 6,031,711, which claims priority from U.S. Provisional Application No. 60/017,609 filed May 15, 1996[, hereby incorporated by reference]. The subject matter of the parent applications are hereby incorporated by reference.

Page 5, line 33 to page 6, line 9:

Two general methods have been employed for making bifunctional chelates form chelating agents. In the first method one or more carboxylic acid groups of a polyaminopolycarboxylic acid chelator are activated by conversion to such activating groups as internal or mixed anhydrides, activated esters (e.g., [p-nitro phenyl] p-nitrophenyl, N-hydroxysuccinimide, etc.) or with other derivatives known to those skilled in the art. The activated acid group is then added to the protein-chelator complex.

Page 11, first chemical formula:



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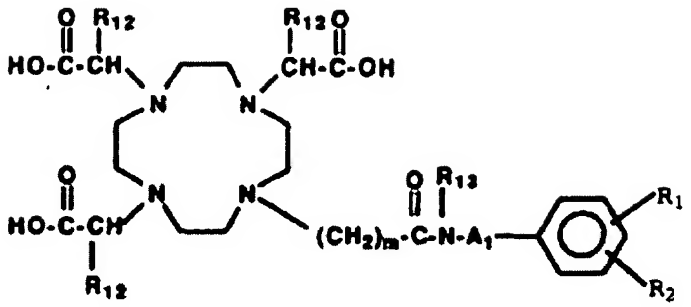

Page 16, line 14 to page 17, line 5:

The methods of linking the bifunctional chelate to the antibody or antibody fragment are known in the art (Brechbiel, same reference as referred to hereinabove) and will depend primarily on the particular bifunctional chelate and secondarily on the antibody or fragment thereof. For example when the formula Ia compound is R_1 = H, R_2 = -NCS or -NHCNHR$_{12}$, one reacts 10 μL of a 5.0 mM aqueous solution of the formula I chelator with 0.5 mL of a 5.0 mg/mL monoclonal antibody (B72.3 purchaseable from Damon Biotech Corporation) in 50 mM Hepes buffer at ph 8.5. 16 μL of 1.5M aqueous triethylamine is added. After 2 hours reaction time, the monoclonal antibody is purified by dialysis. This procedure provides between 1 and 2 formula I chelator molecules bound to each monoclonal antibody. Radioactive metal ion (for example ^{90}Y) can then be added to the monoclonal antibody-bound chelator by methods known in the art. For example, ^{90}Y as the ^{90}Y(III) (acetate)$_3$(H_2O)$_4$ approximate formula in aqueous solution) can be reacted with the monoclonal antibody-bound chelate in solutions where the concentration of each is between 10^{-5} and 10^{-7}M and the pH is 6. Dialysis against citrate is then used to purify the product.

Page 17, lines 6-27:

An alternative, and preferred method follows that described above, but substitutes the metal-chelate complex for the chelating ligand. To use this metal the metal chelate complex is

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

first made by reacting metal-oxide, -halide, -nitrate, -acetate, or the like with formula I chelator. For the chelator described above the acetate of 90^{Y} at $<10^{-6}$M is reacted with the chelator at about 10^{-3}M at pH 6, the chelate complex is purified by ion exchange or reverse phase HPLC chromatography, and then reacted and then reacted with the monoclonal antibody described above for the chelator. The bifunctional, metal-containing, linked antibody is used in the following manner. A human or animal with a tumor to which the monoclonal antibody is specific is injected intravenously, subcutaneously, intraperitoneally or intralymphatically for example, with an aqueous solution of the ^{90}Y-formula I chelator-monoclonal antibody compound. This allows the radioactive metal ion to be directed to the tumor for which it is intended. The intravenous dosage used is 0.1 to 0.4 millicuries per kilogram of body weight.

Page 31, lines 30-31:

A. N,N'-[b]Bis[2-([A]acetyloxy)-1-[(acetyloxy-methyl]-ethyll-5-nitro-1, 3-benzenedicarboxamide

Page 41, lines 2-6:

Data on Water Soluble Gd Complexes and Ions Demonstrating [T]the Enhancement of Relaxivity by [N-Hydroxy-alkyl] N-Hydroxyalkyl or N-alkyl-isophthalamide Groups and by Aryl Groups or by Hydroxyalkyl or Alkylamido Groups.

Page 42, lines 7-8:

A. [N,N'-bis(2-Methylbutyl)] N,N'-Bis(2-methylbutyl)-5-[[(phenylmethoxy)-carbonyl]-amino]-1,3-benzenedicarboxamide

Page 42, lines 26-28:

B. [N,N'-bis(2-Methylbutyl)] N,N'-Bis(2-methylbutyl)-5-[methyl [(phenyl-methoxy)carbonyl]amino]-1,3-benzende-carboxamide

Page 49, lines 16-18:

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

B. 10-[N-([4 **Nitrophenyl]** 4-Nitrophenyl) acetamido]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt

Page 57, lines 16-19:

10-[2-[[3,5-**[**b]Bis[[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid-gadolinium (III) complex

Page 57, lines 21-22:

A. N,N'-**[**b**]**Bis(2-hydroxyethyl)-5-nitro-1,3-benzenedicarboxamide

Page 58, lines 1 and 2:

B. N,N'-**[**b**]**Bis(2-acetoxyethyl)-5-amino-1,3-benzenedicarboxamide

Page 59, lines 10-11:

D. 5-[(**[**c**]**Chloroacetyl)amino]-N,N'-bis(2-hydroxy-ethyl)[-5-amino]-1,3-benzenedicarboxomide

Page 58, lines 13-21:

A solution of N,N'-bis[2-(acetyloxy)ethyl]-5-[(chloroacetyl)amino-1,3-benzenedicarboxamide (6.2 g, 14 mmol) in MeOH (20 mL) was treated with NaOMe (600 mg, 10.5 mmol). After 2 hours at room temperature, the mixture was neutralized with AG-50W-X2 ([H+]H^+ form) resin. The resin was removed by filtration and the solution was evaporated to dryness to afford 4.8 g of crude material. An analytical sample of the title D product was crystallized from MeOH.

Page 59, line 28-31:

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

E. 10-[2-[[3,5-[b]Bis[[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, monosodium salt.

Page 60, lines 22-25:

F. 10-[2-[[3,5-[b]Bis[[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyll]-1,4,7,10-monogadolinium salt (VII).

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
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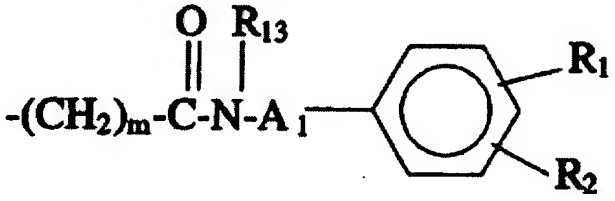
EXHIBIT B

MARKED UP VERSION OF THE AMENDED CLAIMS

1. (amended) A diagnostic agent comprising an aminocarboxylate ligand complexed with a paramagnetic metal ion wherein a nitrogen atom within said aminocarboxylate is substituted with a [substituted aromatic amide] group comprising an aromatic amide containing at least one substitution on the aromatic ring, the substitution comprising a group of 3 or more non-hydrogen atoms.

2. (amended) The diagnostic agent of claim 1 wherein said substituted aromatic amide group is of the formula

I



wherein

A_1 is - $(CH_2)_m$' - or a single bond;

$(CH_2)_m$ and $(CH_2)_m$' may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, [NCS,] $-C-NR_3R_4$, NR_3COR_9

where R_9 is C_4 - C_{18} straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

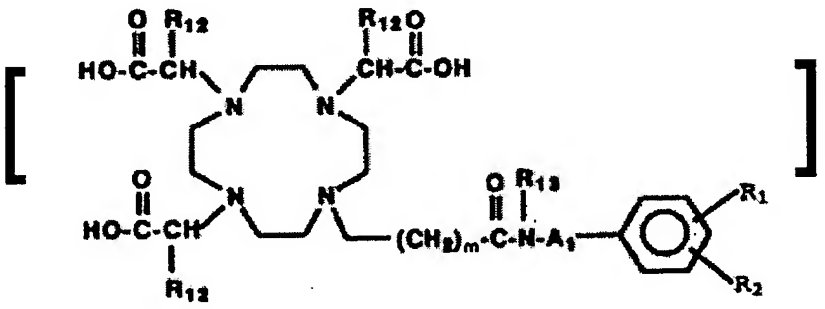
R_{13} is hydrogen, alkyl or arylalkyl, aryl, alkoxy or hydroxyalkyl;

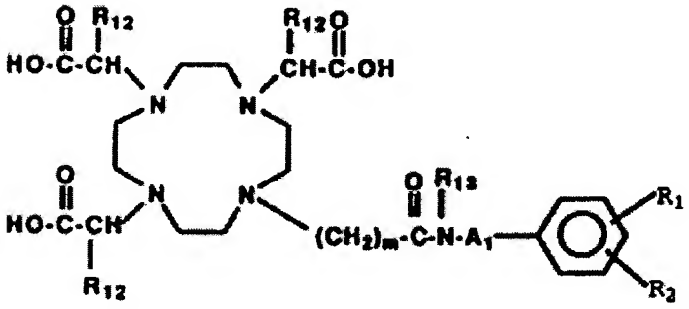
m and m' are independently [1] 0 to 5;

and multimeric forms thereof.

3. (amended) A diagnostic agent of claim 2 wherein said ligand is of the formula

Ia





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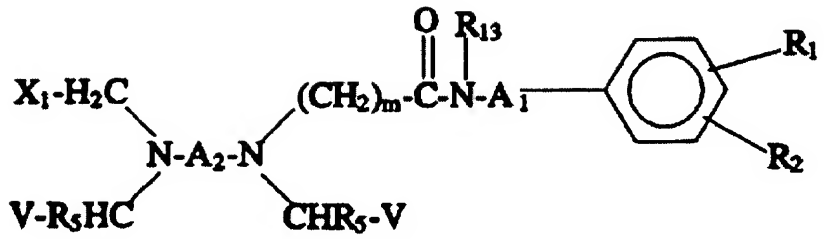
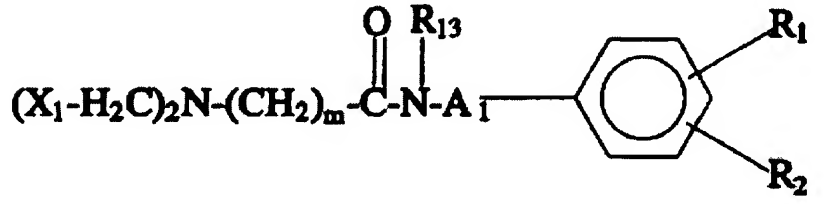
Ib



Ic



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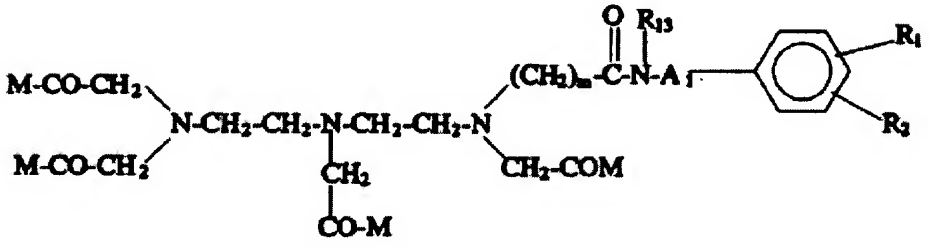
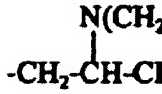
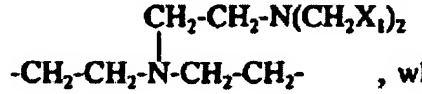


wherein m, R_{13}, A_1, R_1, R_2, and R_{12} are as defined in claim 2 and wherein

X_1 is $-COOY_1$, PO_3HY_1 or $-CONHOY_1$;

Y_1 is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A_2 is $-CHR_6-CHR_7-$, $-CH_2CH_2(ZCH_2-CH_2)_n-$,

 or  , wherein X_1 is as defined above;

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

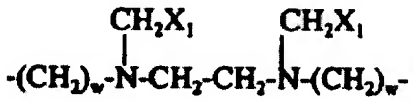
each R_5 is hydrogen or methyl;

R_6 and R_7 together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R_6 is a hydrogen atom and R_7 is a $-(CH_2)_p-C_6-H_4-W$-protein where p is 0 or 1, W is -NH-, $-NHCOCH_2-$ or -NHCS-, protein represents a protein residue;

n is 1, 2 or 3;

Z is an oxygen atom or a sulfur atom or the group NCH_2X_1 or $NCH_2CH_2OR_8$ wherein X_1 is as defined above and R_8 is C_{1-8} alkyl;

V is X_1 or is $-CH_2OH$, $-CONH(CH_2)_rX_1$ or -COB, wherein X_1 is as defined above, B is a protein or lipid residue, r is an integer from 1 to 12, or if R_5, R_6 and R_7 are each hydrogen; then both V's together form the group



where X_1 is as above, w is 1, 2 or 3, provided that at least two of the substituents Y_1 represent metal ion equivalents of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83; from 1 to 4, advantageously 2 or 3, and preferably 2 M's are -OH and the balance independently are $-OR_{10}$, $-NH_2$, $-NHR_{10}$ and/or $NR_{10}R_{10}$' wherein R_{10} and R_{10}' are selected from an organic alkyl radical of up to 18 carbon atoms which may be substituted.

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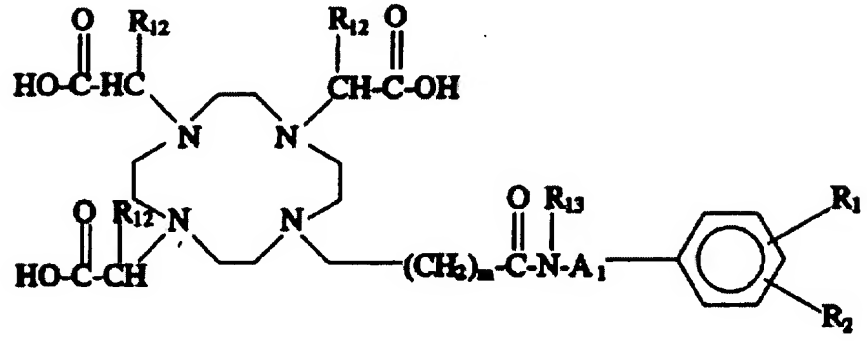
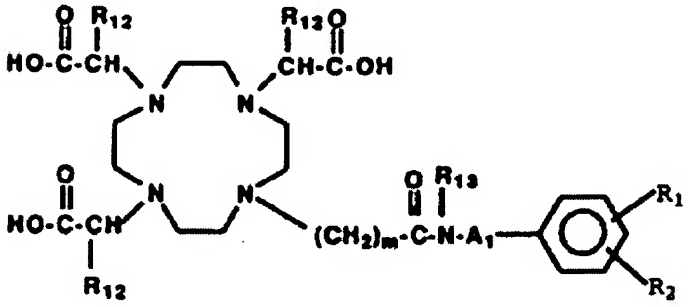
6. (amended) A compound of the formula





wherein

A_1 is $-(CH_2)_{m'}-$ or a single bond;

$(CH_2)_m$ and $(CH_2)_{m'}$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, [NCS,] $-C-NR_3R_4$ and NR_3COR_9 where R_9 is $\underline{C_4-C_{18}}$ straight or branched chain alkyl or hydroxyyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently [1] 0 to 5;

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
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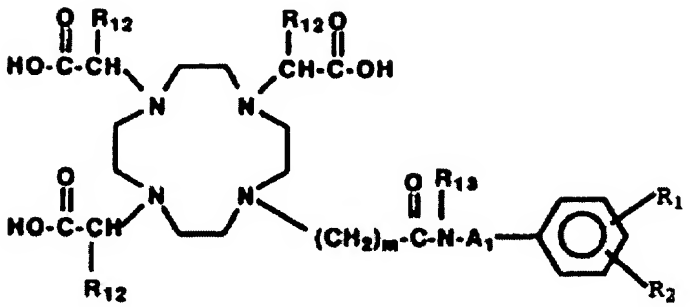
and multimeric forms thereof.

11. (amended) A compound of the formula [of claim 6]



having the name 10-[2-[[3,5-bis[(2,3-dihydroxypropyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid,

wherein

A_1 is -$(CH_2)_m$' - or a single bond;

$(CH_2)_m$ and $(CH_2)_m$' may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, -NHCNHR$_{12}$, -C-NR$_3$R$_4$ and NR$_3$COR$_9$ where R_9 is C_4 -C_{18} straight or branched chain alkyl or hydroxyyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

Express Mail Label No. EL413412686US
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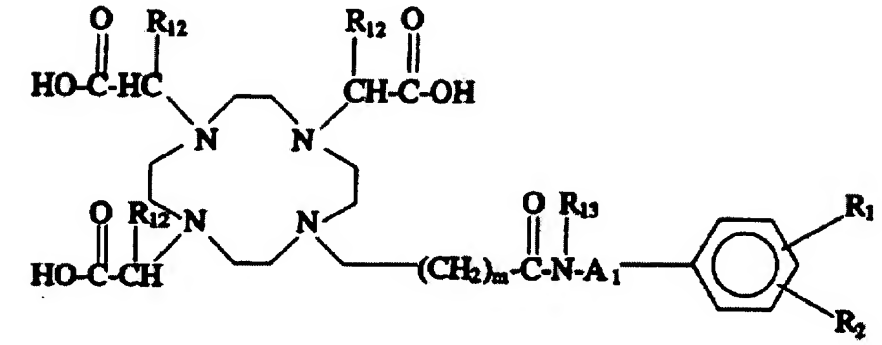
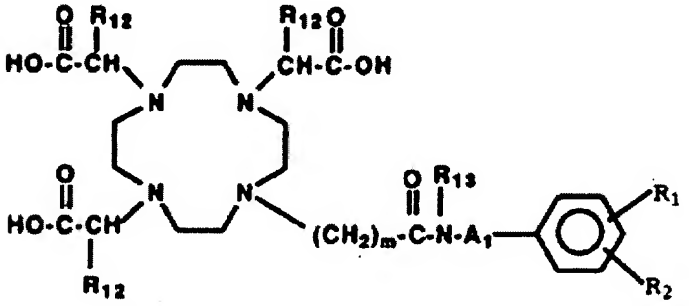
39. A complex or a pharmaceutically acceptable salt of a complex, of a metal atom and a metal chelating ligand having the formula

I





wherein

A_1 is $-(CH_2)_m$'- or a single bond;

$(CH_2)_m$ and $(CH_2)_m$' may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, [NCS] $-C-NR_3R_4$ and NR_3COR_9 where R_9 is C_4 -C_{18} straight or branched chain alkyl or hydroxyyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently [1] 0 to 5;

and multimeric forms thereof.

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
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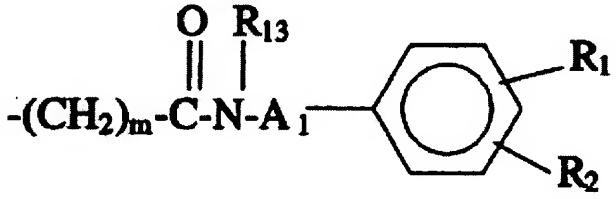
EXHIBIT C

PENDING CLAIMS

1. A diagnostic agent comprising an aminocarboxylate ligand complexed with a paramagnetic metal ion wherein a nitrogen atom within said aminocarboxylate is substituted with a group comprising an aromatic amide containing at least one substitution on the aromatic ring, the substitution comprising a group of 3 or more non-hydrogen atoms.

2. The diagnostic agent of claim 1 wherein said substituted aromatic amide group is of the formula

I



wherein

A_1 is - $(CH_2)_m$' - or a single bond;

$(CH_2)_m$ and $(CH_2)_m$' may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are independently hydrogen,

where R_9 is C_4 - C_{18} a straight or branched chain alkyl or hydroxyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

R_{12} is hydrogen, alkyl or hydroxyalkyl;

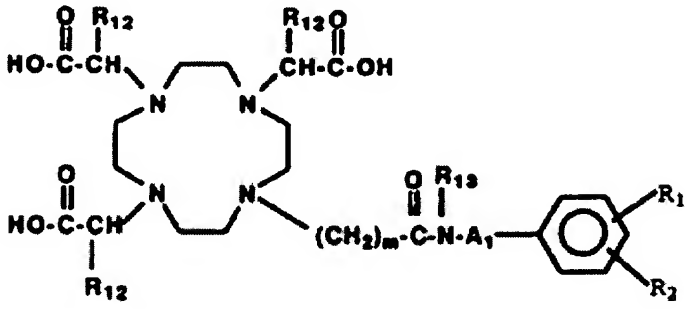
R_{13} is hydrogen, alkyl or arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

3. A diagnostic agent of claim 2 wherein said ligand is of the formula

Ia



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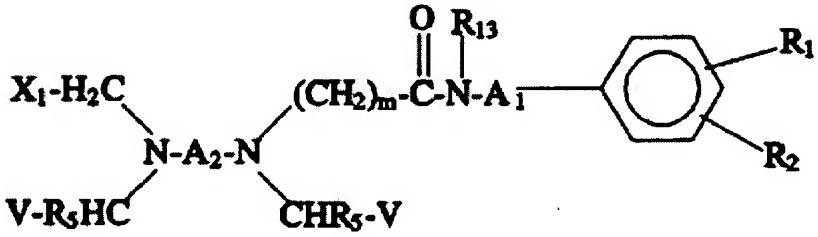

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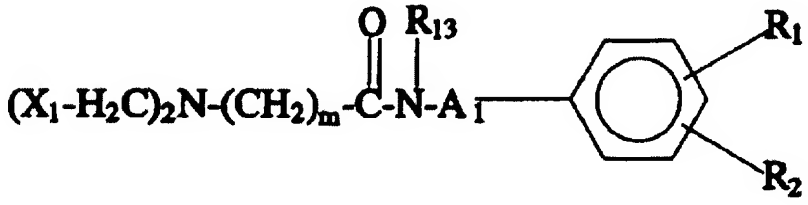

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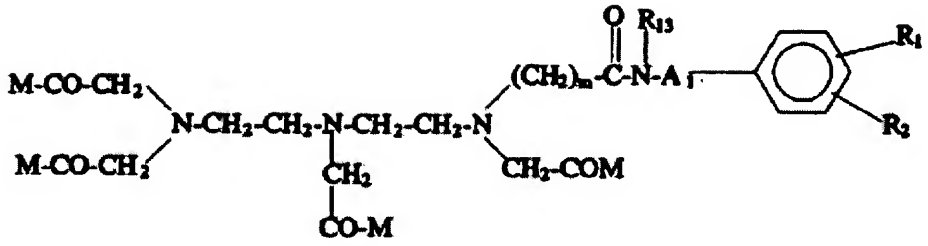
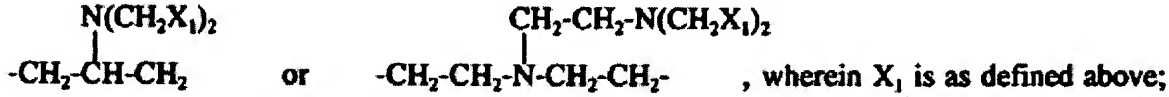


wherein m, R_{13}, A_1, R_1, R_2, and R_{12} are as defined in claim 2 and wherein

X_1 is $-COOY_1$, PO_3HY_1 or $-CONHOY_1$;

Y_1 is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A_2 is $-CHR_6-CHR_7-$, $-CH_2CH_2(ZCH_2-CH_2)_n-$,



each R_5 is hydrogen or methyl;

R_6 and R_7 together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R_6 is a hydrogen atom and R_7 is a $-(CH_2)_p-C_6-H_4-W$-protein where p is 0 or 1, W is -NH-, $-NHCOCH_2-$ or -NHCS-, protein represents a protein residue;

n is 1, 2 or 3;

Z is an oxygen atom or a sulfur atom or the group NCH_2X_1 or $NCH_2CH_2OR_8$ wherein X_1 is as defined above and R_8 is C_{1-8} alkyl;

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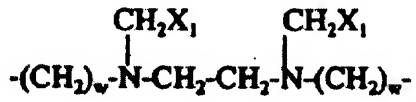
Date Of Deposit: May 29, 2002
KL3:2179663.3

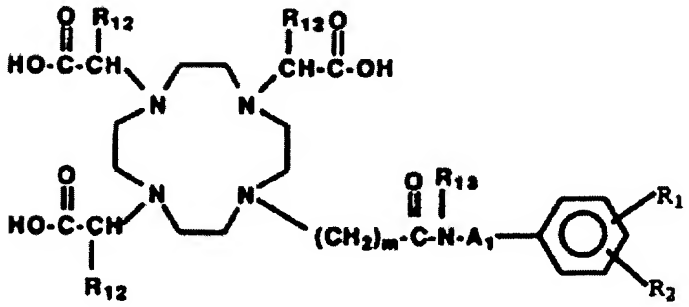
V is X_1 or is $-CH_2OH$, $-CONH(CH_2)_rX_1$ or -COB, wherein X_1 is as defined above, B is a protein or lipid residue, r is an integer from 1 to 12, or if R_5, R_6 and R_7 are each hydrogen; then both V's together form the group



where X_1 is as above, w is 1, 2 or 3, provided that at least two of the substituents Y_1 represent metal ion equivalents of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83; from 1 to 4, advantageously 2 or 3, and preferably 2 M's are -OH and the balance independently are $-OR_{10}$, $-NH_2$, $-NHR_{10}$ and/or $NR_{10}R_{10}$' wherein R_{10} and R_{10}' are selected from an organic alkyl radical of up to 18 carbon atoms which may be substituted.

4. The diagnostic agent of claim 1 wherein said paramagnetic metal ion is gadolinium.

6. A compound of the formula



wherein

A_1 is $-(CH_2)_m$' - or a single bond;

$(CH_2)_m$ and $(CH_2)_m$' may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

alkyl, $-NO_2$, $-NH_2$, $-NHC(=S)NHR_{12}$, $-C(=O)-NR_3R_4$ and NR_3COR_9 where R_9 is C_4 -C_{18} straight or branched chain alkyl or hydroxyyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

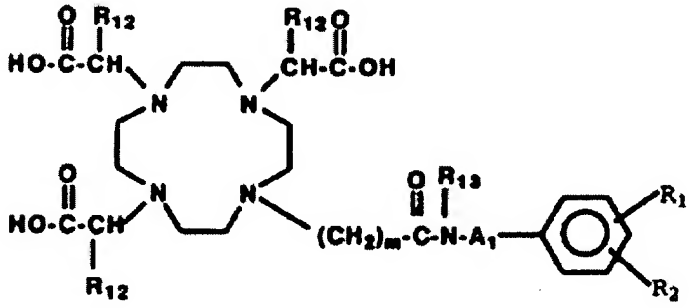
R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

11. (amended) A compound of the formula



having the name 10-[2-[[3,5-bis[(2,3-dihydroxypropyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid,

wherein

A_1 is $-(CH_2)_m'$ - or a single bond;

$(CH_2)_m$ and $(CH_2)_m'$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHC(=S)NHR_{12}$, $-C(=O)-NR_3R_4$ and NR_3COR_9 where R_9 is C_4 -C_{18} straight or branched chain alkyl or hydroxyyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

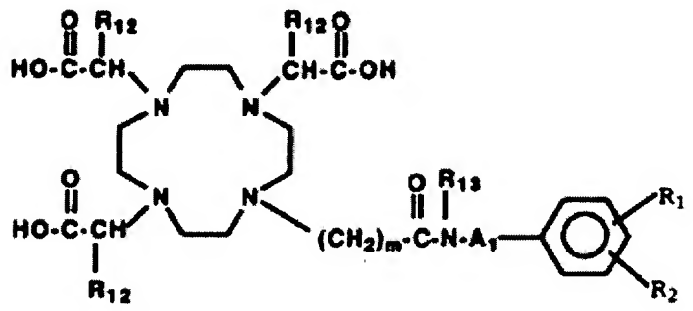
R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

m and m' are independently 0 to 5;

and multimeric forms thereof.

12. The gadolinium complex of the compound of claim 11.

39. A complex or a pharmaceutically acceptable salt of a complex, of a metal atom and a metal chelating ligand having the formula



wherein

A_1 is $-(CH_2)_m'-$ or a single bond;

$(CH_2)_m$ and $(CH_2)_m'$ may independently be substituted with alkyl or hydroxyalkyl;

R_1 and R_2 are each independently hydrogen,

alkyl, $-NO_2$, $-NH_2$, $-NHCNHR_{12}$, $-C-NR_3R_4$ and NR_3COR_9 where R_9 is C_4 -C_{18} straight or branched chain alkyl or hydroxyyalkyl, with the proviso that at least one of R_1 and R_2 must be other than hydrogen;

R_3 and R_4 are independently hydrogen, alkyl, arylalkyl, aryl, alkoxy and hydroxyalkyl;

R_{12} is hydrogen, alkyl or hydroxyalkyl;

R_{13} is hydrogen, alkyl, arylalkyl, aryl, alkoxy or hydroxyalkyl;

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3

m and m' are independently 0 to 5;

and multimeric forms thereof.

Express Mail Label No. EL413412686US
Date Of Deposit: May 29, 2002
KL3:2179663.3